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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/164,568	10/01/1998	RANDOLPH J. NOELLE	012712-572	6823

7278 7590 10/01/2008

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
10/01/2008	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/164,568
Filing Date: October 01, 1998
Appellant(s): NOELLE ET AL.

Bonnie Kramer Carney
For Appellant

EXAMINER'S ANSWER

This is in response to the Appeal Brief filed 02/26/2007 and Substitute "Summary of Claimed Subject Matter" Section to Appeal Brief Filed February 26, 2007, filed 07/11/2007 appealing from the Final Office action mailed 06/14/2006, and in accordance with the Pre-Appeal Conference Pilot Program, wherein the Panel Decision from Pre-Appeal Brief Review was mailed 01/24/2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the Brief.

(2) Related Appeals and Interferences

Appellant states that there are no related applications under appeal or as the subject of an interference that are related to, or would directly affect the pending appeal.

Other than the Panel Decision from the Pre-Appeal Brief Review, mailed 01/24/2007;

the examiner is not aware of any other related appeals, interferences, or judicial proceedings, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the Brief is correct.

This appeal involves claims 82-94.

Claims 1-81 have been canceled previously.

(4) Status of Amendments After Final

Appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the Brief is correct.

Also, see appellant's SUBSTITUTE "SUMMARY OF CLAIMED SUBJECT MATTER" SECTION TO APPEAL BRIEF FILED FEBRARY 26, 2007, filed 07/11/2007.

Appellant's claims recite "human gp39",

wherein "human gp39" is known also as "CD40 ligand or CD40L" as disclosed on page 2, paragraph 3 and page 7 of the instant specification.

"CD40 ligand / CD40L" is known as "CD154" and the prior art reference Lederman et al. (U.S. Patent No. 6,403,091) refers to this molecule as "5C8 / 5C8 antigen".

(6) Grounds of Rejection to be Reviewed on Appeal

Appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the Brief is correct.

(8) Evidence Relied Upon add dates to patents

A) Beschorner et al., U.S. Patent No. 5,597,563, issued 01/28/1997.

B) Cobbold et al., U.S. Patent No. 5,690,933, issued 11/25/1997 .

C) Enyon et al., J. Exp. Med. 175 : 131-138, 1992.

D) Lederman et al., U.S. Patent No. 6,403,091, issued 06/11/2002.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Rejection under 35 U.S.C. § 103(a).

Claims 82-94 stand rejected under 35 U.S.C. § 103 as being unpatentable over Lederman et al. (U.S. Patent No. 6,403,091) in view of Beschorner et al. (U.S. Patent No. 5,597,563), Cobbold et al. (U.S. Patent No. 5,690,933) and Enyon et al. (J. Exp. Med. 175: 131-138, 1992 for the reasons of record.

Lederman et al. teach the treatment of various disease conditions (see entire document) including inhibiting the autoimmune response (column 11, paragraph 7 and Claims) with 5C8- (i.e. CD40L-specific, gp39-specific) antibodies, including monoclonal, chimeric and humanized antibodies (columns 7-8 and Claims) (see entire document).

The primary reference does not explicitly teach the use of administering autoantigen expressing cells and the types of antigen-presenting cells encompassed by the claimed invention.

Enyon et al. teach that B cell presentation of antigen in the absence of appropriate help leads to antigen-specific T cell anergy in vivo (see entire document). Here, Enyon et al. also acknowledge the art-known role of B cells as APCs. It was also known that CD40 the ligand for gp39 (CD40 ligand) is present on other APCs such as dendritic cells, which are intimately involved in the induction of T cell immunity or tolerance. In addition, gp39 was known to be expressed mainly by activated T helper cells and a number of $CD8^+$ cells as well. Therefore, it was known that one could use gp39 antagonists to block T cell-mediated activation and that the appropriate in vivo APCs such as B cells and dendritic cells, which express CD40, would be subject to such manipulation. It was well known in the art at time the invention was made that the provision of signal 1 (antigen) in the absence of signal 2 (help) would lead to some form of tolerance rather than immunity. Enyon et al. Also teach a role for small B cells as antigen-specific tolerizing antigen-presenting cells in acquired self-tolerance soluble self-proteins (see Abstract and last paragraph of Discussion).

Beschorner teach the use of antigen containing antigen-presenting cells for inducing tolerance to autoantigens or self antigens in the treatment of autoimmune diseases by administering the said antigen containing antigen presenting cells and an immunosuppressive (see entire document, including Detailed Description and Claims). Beschorner also teach that the antigen presenting cells include dendritic cells, Langerhans cells and mononuclear phagocytes (see column 6, paragraph 3), encompassed by the claimed methods.

Cobbold et al. teach that specific non-responsiveness can be induced to a self antigen or antigens in order to treat autoimmune diseases by administering immunosuppressive antibodies and antigen (see entire document, including column 3, paragraph 4). Cobbold et al. alo note that persistent antigen is required to maintain tolerance, which applies to self (auto) antigens in the treatment of autoimmune diseases (column 3, paragraph 5).

One of ordinary skill in the art at the time the invention was made would have been motivated to select the combination of an autoantigen containing antigen presenting cells and a gp39-specific antagonist to induce antigen-specific non-responsiveness to autoantigens as a treatment for autoimmunity by providing persistent autoantigens under the cover of immunosuppressives, since both contribute to long term antigen non-responsiveness in the treatment of autoimmunity.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Appellant's arguments in conjunction with various legal citations in the Brief on appeal have been fully considered but have not been found persuasive essentially for the reasons of record.

In the interest of convenience, the Sections set forth herein follow the Brief on Appeal.

Rejection under 35 U.S.C. § 103(a).

Appellant's arguments that the rejection of record has not established any one of the criteria of obviousness, let alone all of the basic criteria of obviousness, have been fully considered but have not been found convincing essentially for the reasons of record.

A. Rejection of Claims 82-94 under 35 U.S.C. § 103, as obvious over Lederman in view of Beschorner, Cobbold and Eynon

Claims 82-94

Appellant argues the following.

The Examiner improperly rejects claims 82-94 as obvious over the combination of Lederman with any of the other cited references. The Examiner has not established a prima facie case of obviousness as set forth by MPEP § 2143 which requires that three basic criteria be met:

(1) the references taken alone or in combination must teach or suggest all of the claimed limitations:

(2) there must be some suggestion and/or motivation in the references or in the general knowledge of one having ordinary skill in the art to modify or combine reference teachings;

and

(3) there must be a reasonable expectation of success.

As shown below, the Examiner has failed to establish any one of the basic criteria, let alone all three.

In contrast to appellant's reliance upon a rigid formula of the teaching-suggestion-motivation test for obviousness, the following is noted.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to inhibit antigen-specific T cell responses in patients / subjects in need (e.g., patients with autoimmune diseases), including those undesirable responses directed towards autoantigens, with CD40L- / gp39-specific antibodies,

incorporating autoantigen-presenting cells in therapeutic regimens with patients with autoimmune diseases undergoing treatment in combination with immunosuppressive CD40L- / gp39-specific antibodies would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing such methods to effectively "reduce antigen-specific T cell responsiveness in vivo" as it reads on the combination of immunosuppressive "CD40L- / gp39-specific antibodies and autoantigen-presenting cells in subjects in need of such treatment".

(1) The Examiner has failed to prove that the cited references either alone or in combination teach all of the limitations of claims 82-94.

Appellant argues the following.

The current claims call for a method that comprises the administration of (a) an antigen- presenting cell (APC) that presents an autoantigen to an activated T cell expressing mouse or human gp39 and (b) an anti-gp39 antibody that binds to mouse or human gp39 on the activated T cell. The prior art cited by the Examiner does not disclose or suggest, either alone or in combination, both steps of the claimed method for reducing antigen-specific T cell responsiveness.

Step (a) - administration of an antigen presenting cell that presents an autoantigen to an activated T cell expressing mouse or human gp39.

Appellant argues the following.

The first step, administration of an APC, is not taught or suggested by the primary reference, Lederman. The Examiner has conceded this fact: Lederman is completely silent as to the administration of APCs to an activated T cell together with an anti-gp39 antibody. See Office Action dated October 22, 2002, page 3. Moreover, Lederman does not provide any functional data using activated T cells.

The Examiner relies upon the secondary references, Beschorner, Cobbold and Eynon, to provide the missing limitation of the use of APCs for the induction of tolerance. However, as shown below, these references do not cure Lederman's defects and are distinguishable from the presently claimed invention.

In contrast to appellant's arguments that the secondary references do not cure Lederman's asserted defects and are distinguishable from the claimed invention,

the following is noted.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981). This appellant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

Also, see MPEP 2145.

Appellant argues that Beschorner teaches the administration of antigen-presenting cells in an environment devoid of mature, activated T cells, subsequent to the use of a generalized immunosuppressive agent (see column 5, paragraph 1 and column 8, paragraph 1 of Beschorner). In addition, appellant asserts that the T cells in Beschorner are not mature and cannot be activated.

However, it appears that appellant ignores the clear teachings of Beschorner of administering antigen presenting cells (e.g., dendritic cells; see Background, Summary of the Invention; Detailed Description, including column 6, paragraph 4; column 7, paragraph 1; and column 9, paragraph 1; Claims 1, 7 and 9 of Beschorner) in combination with antigen (e.g, autoantigen, autoimmune diseases and self-tolerance; see paragraph 2 of the Summary of the Invention on column 4; Detailed Description, including column 6, paragraphs 2 and 5; and Claim 13 of Beschorner) substantially contemporaneously with an immunosuppressive agent (see column 8, paragraph 4 of Beschorner).

While Beschorner may be interested in achieving tolerance to an antigen of interest by administering thymus regenerating agents,

Beschorner teach that under the cover of immunosuppressive therapy, new antigen presenting cells containing the antigen to which the specific tolerance (antigen-specific unresponsiveness) is desired (e.g., see column 5, paragraph 3 of Beschorner) and can be infused simultaneously or shortly thereafter (e.g., see column 2, paragraph 2 in the Background; Detailed Description, including columns 4-5, overlapping paragraph and column 8, paragraph 4; and Claims of Beschorner).

Beschorner also notes that although a thymic regeneration agent may be preferred, it is not necessarily required to practice the invention (e.g., see column 9, lines 22-26 of Beschorner).

Appellant's arguments focusing on cortical thymocytes or immature T cells does not take into account the clear teaching of Beschorner and the understanding of the ordinary artisan of providing an antigen-presenting cell providing an antigen to which tolerance is induced in a recipient under the cover of immunosuppression in order to achieve the desired effect of inducing unresponsiveness to an antigen without inducing a prolonged generalized immune deficiency (e.g., see column 5, paragraphs 4-5 and column 6, paragraph 4 of Beschorner).

The targeted patient population (e.g., a patient with an autoimmune disease) is not devoid of T cells, which subject to immunoregulation under the cover of immunosuppression and antigen-presenting cells, as asserted by appellant.

This is implicit in the basic teachings of Beschorner of treating patients with certain ongoing diseases or conditions and accompanying ongoing activated immune responses (e.g., a patient with autoimmunity) under the umbrella of a therapeutic regimen of immunosuppression and antigen-presenting cells

as well as the teachings of Cobbold et al. that specific non-responsiveness can be induced to a self-antigen(s) in order to treat autoimmune diseases by administering immunosuppressive antibodies and antigen and the importance of persistent antigen in such therapeutic regimens (see the teachings of Cobbold et al. described herein in this Section below).

Again, Beschorner teach the use of antigen containing antigen-presenting cells for inducing tolerance to autoantigens or self antigens in the treatment of autoimmune diseases by administering the said antigen containing antigen-presenting cells and an immunosuppressive (see entire document, including Detailed Description and Claims of Beschorner). Beschorner also teach that the antigen-presenting cells include dendritic cells, Langerhans cells and mononuclear phagocytes (see column 6, paragraph 3 of Beschorner), encompassed by the claimed methods. While Beschorner is directed to a goal of inducing antigen-specific tolerance while minimizing risk to the animal that is normally associated with protracted immunosuppressive therapy, Beschorner acknowledges that immunosuppressive therapy was the standard therapy at the time the invention was made (see Background of the Invention and Summary of the Invention of Beschorner).

For example, as indicated in the Background, Beschorner teaches that unwanted immune reactions which can result in autoimmune disease can be inhibited by a variety of immunosuppressives, including anti-T cell antibodies, including antibodies to T cell subpopulations (e.g., see column 2, paragraph 1 of Beschorner).

Therefore in contrast to appellant's narrow reading of the prior art,

the teachings of Beschorner are consistent with the teachings of treating autoimmune disease with immunosuppressive anti-T cell antibodies, such as the immunosuppressive CD40L-/gp39-specific antibodies (Lederman et al.) as well as the role and provision of antigen-presenting cells in inducing antigen-specific unresponsiveness to an antigen of interest, such as an autoantigen, in the context of patients with autoimmune diseases (see paragraph 2 of the Summary of the Invention on column 4; Detailed Description, including column 6, paragraphs 2 and 5; and Claim 13 of Beschorner).

In contrast to appellant's assertions that Cobbold et al.'s teachings are misplaced, since Cobbold et al. is silent as to the administration of antigen-presenting cells and to the administration of anti-gp39 (anti-CD40L antibodies) and that Cobbold et al.'s teachings are limited to the administration of anti-CD4 and anti-CD8 antibodies in the context of skin graft rejections,

the following is noted.

As noted previously, Cobbold et al. teach that specific non-responsiveness can be induced to a self-antigen(s) in order to treat autoimmune diseases by administering immunosuppressive antibodies and antigen (see entire document, including column 3, paragraph 4 of Cobbold et al.).

Cobbold et al. also note that persistent antigen is required to maintain tolerance, which applies to self (auto) antigens in the treatment of autoimmune diseases (see column 3, paragraph 5 of Cobbold et al.).

Here, while Cobbold et al. teach that antigen reminders can be given at regular intervals (e.g., in the case of extraneous foreign antigens such as allergens) (see column 3, paragraph 5 of Cobbold et al.);

Beschorner provides the teachings of providing an autoantigen(s) of interest via antigen-presenting cells under the cover of immunosuppressive therapy in the treatment of autoimmune diseases (see above in this Section concerning the teachings of Beschorner).

Appellant acknowledges that the provision of persistent antigen in transplantation is the tissue graft itself (see column 3, paragraph 5 of Cobbold et al.).

The ordinary artisan would have recognized that autoantigen-presenting cells, as taught by Beschorner, would serve the same purpose of providing persistent antigen, antigen reminders or antigen in combination with immunosuppression in patients with autoimmune diseases, as taught by Cobbold et al.

Furthermore, the CD40L (i.e., gp39) was not known at the priority date of Cobbold et al.

Therefore, Cobbold et al. could not have been expected to teach the CD40L / gp39 specificity.

Beschorner also has an effective priority date (e.g., 1992) after Cobbold et al. (e.g., see Foreign Priority date of 1989).

Cobbold et al. do direct the ordinary artisan towards the use of immunosuppressive antibodies that are directed to CD4-expressing T cells, which are the same T cell subpopulation targeted by Lederman et al. in the use of anti-CD40L / anti-5C8 antibodies (anti-gp39 antibodies) in the treatment of autoimmunity.

Therefore, in contrast to appellant's assertions, Cobbold et al. provides direction to inducing tolerance / antigen-specific unresponsiveness via the inhibition of T cells by the administration of immunosuppressive anti-T cell antibodies in the presence of antigen, including its application to patients with autoimmune diseases.

Beschorner teaches an alternative means (antigen-presenting cells) to provide persistent antigen, antigen reminders or antigen of interest at the time of administering immunosuppressive agents, such as immunosuppressive anti-T cell antibodies.

Appellant argues that Enyon et al. do not provide a teaching of administering antigen-presenting cells and is limited to unprimed T cell and not to activated T cells expressing gp39 / CD40L.

As pointed out previously, Enyon et al. was provided to note that B cells were antigen-presenting cells (e.g. see instant Claims 83-86). Consistent with the understanding of the ordinary artisan at the time the invention was made, Enyon et al. teach that B cell presentation of antigen in the absence of appropriate help leads to antigen-specific T cell anergy in vivo (see entire document, including page 131, column 1, paragraph 1; page 136, column 2, paragraphs 1-2). Here, Enyon et al. also acknowledge the art-known role of B cells as APCs, including B cell involvement in tolerance induction in skin graft survival (see page 131, column 2, paragraph 1). Enyon et al. also note that antigen-specific B cells are involved in tolerance induction (page 132, column 1, lines 11-17).

Again, the teachings of Enyon et al. provided, simply in part, to provide for the known two-signal hypothesis of anergy (tolerance / antigen-specific unresponsiveness) and for the known role of B cells as antigen-presenting cells by the ordinary artisan at the time the invention was made,

which is consistent with the Background of the Invention on pages 1-2 of the instant specification.

Background of the Invention

To induce antigen-specific T cell activation and clonal expansion, two signals provided by antigen-presenting cells (APCs) must be delivered to the surface of resting T lymphocytes (Jenkins, M. and Schwartz, R. (1987)J. Exp. Med. 165, 302-319; Mueller, D.L., et al. (1990) J. Immunol. 144, 3701-3709; Williams, I.R. and Unanue, E.R. (1990) Immunol. 145, 85-93). The first signal, which confers specificity to the immune response, is mediated via the T cell receptor (TCR) following recognition of foreign antigenic peptide presented in the context of the major histocompatibility complex (MHC). The second signal, termed costimulation, induces T cells to proliferate and become functional (Schwartz, R.H. (1990) Science 248, 1349-1356). Costimulation is neither antigen-specific, nor MHC restricted and is thought to be provided by one or more distinct cell surface molecules expressed by APCs (Jenkins, M.K., et al. (1988) J. Immunol. 140, 3324-3330; Linsley, P.S., et al. (1991) J. Exp. Med. 173,721-730; Gimmi, C.D., et al., (1991) Proc. Natl. Acad. Sci. USA. 88, 6575-6579; Young, J.W., et al. (1992) J. Clin. Invest. 90, 229-237; Koulova, L., et al. (1991) J. Exp. Med. 173, 759-762; Reiser, H., et al. (1992) Proc. Natl. A cad. Sci. USA. 89, 271-275; van-Seventer, G.A., et al. (1990) J. Immunol. 144, 4579-4586; LaSalle, J.M., et al., (1991) J.

Immunol. 147, 774-80; Dustin, M.I., et al., (1989) J. Exp. Med. 169, 503; Armitage, R.J., et al. (1992) Nature 357, 80-82; Liu, Y., et al. (1992) d. Exp. Med. 175, 437-445). One costimulatory pathway involved in T cell activation involves the molecule CD28 on the surface of T cells. This molecule can receive a costimulatory signal delivered by a ligand on B cells or other APCs. Ligands for CD28 include members of the B7 family of B lymphocyte activation antigens, such as B7-1 and/or B7-2 (Freedman, A.S. et al. (1987) Immunol. 137, 3260-3267; Freeman, G.J. et al. (1989)J. Immunol. 143, 2714-2722; Freeman, (G.J. et al. (1991) J. Exp. Med. 174, 625-631; Freeman, G.J. et al. (1993) Science 262, 909- 911; Azuma, M. et al. (1993) Nature 366, 76-79; Freeman, G.J. et al. (1993) J. Exp. Med. 178, 2185-2192). B7-1 and B7-2 are also ligands for another molecule, CTLA4, present on the surface of activated T cells, although the role of CTLA4 in costimulation is unclear.

Delivery of an antigen-specific signal with a costimulatory signal to a T cell leads to T cell activation, which can include both T cell proliferation and cytokine secretion. In contrast, delivery of an antigen-specific signal to a T cell in the absence of a costimulatory signal is thought to induce a state of unresponsiveness or anergy in the T cell, thereby inducing antigen-specific tolerance in the T cell.

In contrast to appellant's continual assertions concerning the limitations of Enyon as to being deficient in terms of the claimed therapeutic regimens,

Enyon et al. does provide sufficient motivation and expectation of success that B cells, including both antigen-specific B cells and small resting B cells can serve as antigen presenting cells in tolerizing regimens vivo (see entire document, including page 131, column 1, paragraph 1; page 136, column 2, paragraphs 1-2).

For example, Enyon et al. teach a role for small B cells as antigen-specific tolerizing antigen-presenting cells in acquired self-tolerance soluble self-proteins (see Abstract and last paragraph of Discussion).

Also, it is noted that Enyon et al. published contemporaneously with the discovery of CD40L / gp39 (e.g., see page 2, paragraph 3 of the instant specification).

Enyon et al. is concerned with B cells as antigen-presenting cells and not with all of the accessory / costimulatory molecules or therapeutic regimens associated with said B cells.

Therefore, in contrast to appellant's narrow reading of Enyon et al.,

the role of B cells as antigen-presenting cells, as claimed, was known to the ordinary artisan at the time the invention was made and, in turn, would have been an obvious substitution or functional equivalent of the antigen-presenting cells, taught by Beschorner.

The prior art is consistent with the delivery of an antigen-specific signal to a T cell in the absence of a costimulatory signal in order to induce a state of tolerance or antigen-specific unresponsiveness in the T cell.

Here, the autoantigen-presenting cells provide the antigen-specific signal and the immunosuppressive anti-CD40L / anti-gp39 antibodies inhibit the appropriate signaling in T cells, resulting in antigen-specific unresponsiveness or a reduction in antigen-specific responsiveness.

Step (b) – co-administration of an anti-gp39 antibody which binds to mouse or human gp39 on the activated T cell.

Appellant argues the following.

The second step of the method- the administration of an anti-gp39 antibody- is also not taught or suggested by any of the cited references. All of the secondary references are silent as to the administration of an anti-gp39 antibody. The Examiner argues that "the teachings of Lederman et al. clearly provides for anti-CD40L (anti-5c8, anti-gp39, anti-CD40 ligand) antibodies to inhibit the immune response in order to treat disease conditions, such as autoimmunity." See Office Action dated June 14, 2006, page 5. However, the Lederman teachings do not teach a person of skill in the art to treat an autoimmune disease because the model systems used in Lederman are flawed. There are no data anywhere in Lederman showing the effect of monoclonal antibody 5c8 on autoimmune responses or autoimmune diseases. Also, there are no data showing the effect of normal human T cells expressing what is called T-BAM on an antigen-specific immune response in vitro or in vivo.

While appellant attempts to dismiss the teachings of Lederman et al. with respect to treating disease conditions such as autoimmunity,

appellant clearly ignores the following on column 11, paragraph 7 of Lederman et al.

> In another embodiment of this invention, inhibiting the immune response of an animal is valuable as a method of inhibiting the autoimmune response in an animal suffering from autoimmune disease. Examples of autoimmune diseases include, but are not limited to, rheumatoid arthritis, Myasthenia gravis, systemic lupus erythematosus, Graves' disease, idiopathic thrombocytopenia purpura, hemolytic anemia, diabetes mellitus and drug-induced autoimmune diseases, e.g., drug-induced lupus.

While appellant makes assertions concerning the applicability of Jurkat T cells in the treatment of autoimmunity with respect to the teachings of Lederman et al.,

appellant ignores that the purpose of the in vitro assays, including the use of Jurkat T cells, was to test the ability of the 5C8-specific / CD40L-specific / gp39-specific antibodies to inhibit T cell - B cell interactions and activation.

For example, see column 11, paragraph 2 of Lederman et al.

> This invention provides a method of inhibiting B cell activation in an animal which comprises administering to the animal an effective inhibiting amount of a pharmaceutical composition comprising the monoclonal antibody which specifically recognizes the activated T cell surface protein and a pharmaceutically acceptable carrier. For the purposes of this invention, an "effective inhibiting amount" of a pharmaceutical composition is any amount of the pharmaceutical composition which is effective to bind to a protein on the surface of activated T cells and thereby inhibit T cell activation of B cells. In one embodiment of this invention, the B cells are resting B cells. In another embodiment of this invention, the B cells are primed B cells.

Testing T cell – B cell interactions in this manner is consistent with the procedures and the analysis of the ordinary artisan in the art at thee time the invention was made

and acknowledged in the Background of the Invention on page 2, paragraph 2 of the instant specification.

Interactions between T cells and B cells play a central role in immune responses. Induction of humoral immunity to thymus-dependent antigens requires "help" provided by T helper (hereafter Th) cells. While some help provided to B lymphocytes is mediated by soluble molecules released by Th cells (for instance lymphokines such as IL-4 and IL-5), activation of B cells also requires a contact-dependent interaction between B cells and Th cells. Hirohata et al., J. Immunol., 140:3736-3744 (1988); Bartlett et al., J. Immunol., 143:1745-1754 (1989). This indicates that B cell activation involves an obligatory interaction between cell surface molecules on B cells and Th cells. The molecule(s) on the T cell therefore mediates contact-dependent helper effector functions of T cells. A contact-dependent interaction between molecules on B cells and T cells is further supported by the observation that isolated plasma membranes of activated T cells can provide helper functions necessary for B cell activation. Brian, Proc. Natl. Acad. Sci. USA, 85:564-568 (1988); Hodgkin et al., J. Immunol., 145:2025-2034 (1990); Noelle et al., J. Immunol., 146:1118- 1124 (1991).

Also, as indicated in the previous Section with respect to the role of B cell as antigen-presenting cells,

Enyon et al. does provide sufficient motivation and expectation of success that B cells, including both antigen-specific B cells and small resting B cells can serve as antigen presenting cells in tolerizing regimens.

While Lederman et al. describes the role of anti-CD40L / anti-gp39 / anti-5C8 antibodies in the inhibiting T cell - B cell interactions and activation,

the teachings of the role of B cells as antigen-presenting cells as taught by Enyon et al. are consistent with the teachings of the prior art of providing antigen-presenting cells (e.g., B cells) under the cover of or in combination with immunosuppressive agents, such as immunosuppressive antibodies in order to induce tolerance / antigen-specific unresponsiveness to the ordinary artisan at the time the invention was made (see Beschorner).

Also, the teachings of immunosuppressive anti-CD40L / anti-gp39 / anti-5C8 antibodies are consistent with the teachings of Beschorner and Cobbold et al. with respect to the administration of immunosuppressive anti-T cell antibodies, including immunosuppressive anti-CD4 T cell antibodies, in an environment with autoantigen to induce tolerance / antigen-specific unresponsiveness.

With respect to appellant's assertions concerning the reliance of the model systems in Lederman et al. for in vivo treatment,

appellant is reminded that the claims of Lederman et al. (U.S. Patent No. 6,403,091) are drawn to methods of treatment, even though methods of treatment were not exemplified in the specification.

U.S. patents are presumed valid by U.S. courts unless proven otherwise. See 35 U.S.C. 282.

Further, it is noted that the claims of Lederman et al. are drawn to methods of inhibiting transplant rejection, a hallmark of cell-mediated immunity, that is, immunity associated with T cells.

Further, it is noted that while the Examples of the instant specification involve inducing antigen-specific unresponsiveness in the context of allogeneic B cells and bone marrow,

there are no working examples of inducing antigen-specific unresponsiveness in the context of autoantigens in the instant application.

It appears that appellant may be applying a double-standard for actual reduction to practice with respect to the teachings of Lederman et al.

Also, the nature of the autoimmune diseases described by Lederman et al. (see column 11, paragraph 2 of Lederman et al.; also, see excerpt above herein in this Section) involves cell-mediated or T cell-mediated immunity or interactions.

Although the instant specification does not appear to describe any particular autoimmune disease,

the targeted conditions described and claimed by Lederman et al. (e.g., transplant rejection, autoimmunity, allergy) (see column 11, paragraphs 6-8 of Lederman et al.) are consistent with the instant disclosure (autoimmune disorders, allergy, transplantation) (e.g., see pages 13-14, overlapping paragraph of the instant specification).

Appellant has not distinguished the diseases targeted between Lederman et al. and the instant application.

Attorney arguments cannot take the place the evidence lacking in the record. Meitzner v. Mindick, 193 USPQ 17, 22 (CCPA 1977).

(2) The Examiner has failed to cite references or general knowledge that would suggest or motivate one having ordinary skill in the art to modify or combine the reference teachings to arrive at the invention claimed in claims 82-94.

In contrast to appellant's assertions that the correct standard for combining prior art references requires that each reference must provide some suggestion or motivation to combine those features identified by the examiner to arrive at the claimed invention,

appellant's reliance upon a rigid teaching-suggestion-motivation rationale to support obviousness has not been found convincing.

While a rigid teaching-suggestion-motivation rationale may be used to support an obviousness rejection,

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to inhibit antigen-specific T cell responses in patients / subjects in need (e.g., patients with autoimmune diseases), including those undesirable responses directed towards autoantigens, with immunosuppressive CD40L- / gp39-specific antibodies, incorporating autoantigen-presenting cells in therapeutic regimens with patients with autoimmune diseases undergoing treatment with immunosuppressive CD40L- / gp39-specific antibodies would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing such methods to effectively "reduce antigen-specific T cell responsiveness in vivo" as it reads on the combination of "CD40L / gp39-specific antibodies and autoantigen-presenting cells in subjects in need of such treatment".

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support the rejection under 35 U.S.C. 103(a) are noted:

As indicated above in **Section (1) Step(a) above**, the following should be kept in mind (*citations to references can be found above*).

Beschorner clearly teach administering antigen presenting cells (e.g., dendritic cells) in combination with antigen (e.g, *autoantigen, autoimmune diseases and self-tolerance*) substantially contemporaneously with an immunosuppressive agent.

Beschorner teach that under the cover of immunosuppressive therapy, *new antigen presenting cells* containing the antigen to which the specific tolerance (antigen-specific unresponsiveness) is desired can be infused simultaneously or shortly thereafter.

Beschorner also notes that although a thymic regeneration agent may be preferred, it is not necessarily required to practice the invention (e.g., see column 9, lines 22-26 of Beschorner).

Cobbold et al. teach that specific non-responsiveness can be induced to a *self-antigen or antigens in order to treat autoimmune diseases* by administering immunosuppressive antibodies and antigen and that persistent antigen is required to maintain tolerance, which applies to *self (auto) antigens in the treatment of autoimmune diseases.*

While Cobbold et al. teach antigen reminders can be given at regular intervals (e.g., in the case of extraneous foreign antigens such as allergens),

Beschorner provides the teachings of providing an autoantigen(s) of interest via antigen-presenting cells under the cover of immunosuppressive therapy in the treatment of autoimmune diseases.

The ordinary artisan would have recognized that autoantigen-presenting cells (Beschorner) would serve the same purpose as providing persistent antigen, antigen reminders or antigen at the time of immunosuppression in patients with autoimmune diseases (Cobbold et al.).

The prior art is consistent with the delivery of an antigen-specific signal to a T cell in the absence of a costimulatory signal in order to induce a state of tolerance or antigen-specific unresponsiveness in the T cell.

Here, the autoantigen-presenting cells provide the antigen-specific signal and the immunosuppressive anti-CD40L / anti-gp39 antibodies inhibit the appropriate signaling in T cells, resulting in antigen-specific unresponsiveness or a reduction in antigen-specific responsiveness.

A) Combining prior art elements according to known methods to yield predictable results.

The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements (immunosuppressive anti-CD40L / anti-gp39 antibodies to treat autoimmunity and antigen-presenting cells employed in the induction of tolerance / antigen-specific unresponsiveness in the treatment of autoimmune diseases) were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods (the combination of immunosuppressives, including immunosuppressive antibodies, and autoantigen-presenting cells) with no change in their respective functions and the combination would have yielded nothing more than predictable results of providing a therapeutic effect of "reducing antigen-specific T cell responsiveness in vivo to an antigen (e.g., autoantigen) in a subject patient in need (e.g., a patient with an autoimmune disease)".

B) Simple substitution of one known element for another to obtain predictable results.

The rationale to support a conclusion that the claims would have been obvious is that the substitution of one known element (existing immunosuppressive agents, including anti-T cell antibodies, as well as anti-T cell antibodies that target $CD4^+$ T cells) with another (e.g. anti-CD40L / anti-gp39 antibodies) would have yielded predictable results of inducing providing a therapeutic effect of reducing antigen-specific T cell responsiveness in vivo to an antigen (e.g., autoantigen) in a subject patient in need (e.g., a patient with an autoimmune disease) via the combination of immunosuppressives, including immunosuppressive antibodies, and autoantigen-presenting cells in inducing tolerance / unresponsiveness to an antigen of interest (e.g., autoantigen) to one of ordinary skill in the art at them time of the invention.

Alternatively, the rationale to support a conclusion that the claims would have been obvious is that the substitution of one known element (e.g. immunosuppressive anti-CD40L / anti-gp39 antibodies in the treatment of autoimmunity) with another (combination of immunosuppressive agents, including anti-T cell antibodies, as well as anti-T cell antibodies that target $CD4^+$ T cells and autoantigen-presenting cells) would have yielded predictable results of providing a therapeutic effect of "reducing antigen-specific T cell responsiveness in vivo to an antigen (e.g., autoantigen) in a subject patient in need (e.g., a patient with an autoimmune disease)" via the combination of immunosuppressives, including immunosuppressive antibodies, and autoantigen-presenting cells in inducing tolerance / unresponsiveness to an antigen of interest (e.g., autoantigen) to one of ordinary skill in the art at them time of the invention.

C) Use of known technique to improve similar products in the same way.

The rationale to support a conclusion that the claims would have been obvious is that a method of employing antigen-presenting cells to induce tolerance / unresponsiveness to an antigen of interest was made part of ordinary capabilities (e.g. provide antigen-presenting cells with immunosuppressive agents, such as anti-T cell antibodies) of one skilled in the art based upon the teachings of Beschorner. One of ordinary skill in the art would have been capable of applying the known methods of employing immunosuppressive anti-CD40L / anti-gp39 antibodies in the treatment to provide the immunosuppressive anti-T cell antibody, and the results would have been predictable to one of ordinary skill in the art of providing a therapeutic effect of "reducing antigen-specific T cell responsiveness in vivo to an antigen (e.g., autoantigen) in a subject patient in need (e.g., a patient with an autoimmune disease)" via the combination of immunosuppressive, including immunosuppressive antibodies, and autoantigen-presenting cells in inducing tolerance / unresponsiveness to an antigen of interest (e.g., autoantigen).

Also, note that Cobbold et al. teach that persistent antigen is required to maintain tolerance, which applies to self (auto) antigens in the treatment of autoimmune diseases (column 3, paragraph 5 of Cobbold et al.) and that anti-T cell antibodies that are directed to $CD4^+$ T cells are employed in methods to induce tolerance / antigen-specific unresponsiveness via the inhibition of T cells.

The administration of autoantigen-presenting cells as taught by Beschorner would have provided the persistent antigen, antigen reminders or antigen at the time of immunosuppression, as taught by Cobbold et al., in the treatment of autoimmune diseases.

D) Applying a known technique to a known product ready for improvement to yield predictable results.

The rationale to support a conclusion that the claims would have been obvious is that a particular known technique (combination of an immunosuppressive agent, including immunosuppressive anti-T cells antibodies and autoantigen-presenting cells) was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known product (e.g. immunosuppressive anti-CD40L / anti-gp39 antibody) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

Alternatively, the rationale to support a conclusion that the claims would have been obvious is that a particular known technique (immunosuppressive CD40L- / gp39-specific antibodies in the treatment of autoimmunity) was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known product (combination of an immunosuppressive agent, including immunosuppressive anti-T cells antibodies and autoantigen-presenting cells) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

E) "Obvious to try" --- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (combination of an immunosuppressive agent, including immunosuppressive anti-T cells antibodies and autoantigen-presenting cells) within his or her technical grasp. This leads to the anticipated success of employing an immunosuppressive anti-CD40L / anti-gp39 antibody that inhibits T cells, particularly $CD4^+$ T cells in combination with autoantigen-presenting cells, it is likely the product not of innovation but of ordinary skill and common sense.

Alternatively, the rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (an immunosuppressive anti-CD40L / anti-gp39 antibody that inhibits T cells, particularly $CD4^+$ T in the treatment of autoimmunity) within his or her technical grasp. This leads to the anticipated success of employing the combination of an immunosuppressive agent, including immunosuppressive anti-T cells antibodies and autoantigen-presenting cells, it is likely the product not of innovation but of ordinary skill and common sense.

F) Some teachings, suggestion, or motivation in the prior art that would have lead one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

Since the combination of an immunosuppressive agent, including immunosuppressive anti-T cells antibodies and autoantigen-presenting cells in the induction of tolerance / antigen-specific unresponsiveness to a patient with autoimmunity would have been predictable at the time of the invention, there would have been reasonable expectation of successful development of employing an immunosuppressive anti-CD40L / anti-gp39 antibody that inhibits T cells, particularly $CD4^+$ T cells, in combination with autoantigen-presenting cells in the induction of tolerance / antigen-specific unresponsiveness to a patient with autoimmunity, as claimed. The prior art had recognized the obstacles to be overcome in development of inducing tolerance / antigen-specific unresponsiveness to an antigen of interest (e.g., autoantigen), and had suggested a finite number of therapeutic regimens to overcome this obstacles. The claims were obvious because it would have been obvious to try the known methods of combination of an immunosuppressive agent, including immunosuppressive anti-T cells antibodies and autoantigen-presenting cells in the induction of tolerance / antigen-specific unresponsiveness to a patient with autoimmunity with a reasonable expectation of success.

In this case, a person of ordinary skill has good reason to pursue the known options, e.g. substituting the immunosuppressive anti-CD40L / anti-gp39 antibody as the immunosuppressive agent or anti-T cell antibody in the combination of an immunosuppressive in combination with an autoantigen-presenting cell, or in the alternative, substituting the combination of an immunosuppressive anti-T cell antibody and an autoantigen-presenting cells as the immunosuppressive regimen rather than relying upon immunosuppressive anti-CD40L / anti-gp39 antibody alone, within his or her technical grasp with reasonable expectation of success.

Contrary to appellant's argument that the references teaches away from the claimed invention, it is noted that a prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the appellant." See In re Haruna, 249 F.3d 1327, 58USPQ2d 1517 (Fed. Cir. 2001).

Also, see In re Gurley, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

General skepticism of those in the art -- not amounting to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. Gillette Co. v. S.C. Johnson & Son, Inc., 16 USPQ2d 1923, 1929 (Fed. Cir. 1990).

In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art.

Here, there is no discouragement of administering autoantigen-presenting cells in combination with immunosuppressive anti-T cell antibodies, such as immunosuppressive anti-CD40L / anti-gp39 antibodies, in the treatment with patients with autoimmune diseases in order to reduce antigen-specific T cell responses to autoantigens.

Given that the prior art goal was to inhibit autoimmune responses via immunosuppression and more particularly, to induce antigen-specific unresponsiveness ,

incorporating the combination of an immunosuppressive agent, including an immunosuppressive anti-T cell antibody such as anti-CD40L / anti-gp39 antibodies in combination with autoantigen-expressing cells in the induction of tolerance / antigen-specific unresponsiveness to a patient with autoimmunity would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing therapeutic regimens to provide a therapeutic effect of "reducing antigen-specific T cell responsiveness in vivo to an antigen (e.g., autoantigen) in a subject patient in need (e.g., a patient with an autoimmune disease)" via the combination of immunosuppressive, including immunosuppressive antibodies, and autoantigen-presenting cells in inducing tolerance / unresponsiveness to an antigen of interest (e.g., autoantigen).

In conclusion, given that the prior art teaches providing immunosuppression, including immunosuppressive anti-T cell antibodies, and autoantigen to treat patients with autoimmunity, it would have been obvious to one of skill in the art at the time of the invention to achieve the predictable results of "reducing antigen-specific T cell responsiveness in vivo to an antigen (e.g., autoantigen) in a subject patient in need (e.g., a patient with an autoimmune disease)" via the combination of immunosuppressive anti-CD40L / anti-gp39 antibodies and autoantigen-presenting cells in inducing tolerance / antigen-specific unresponsiveness to an antigen of interest (e.g., autoantigen).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(3) The Examiner has failed to cite references that rise to a reasonable expectation of success in achieving the invention claimed in claims 82-94.

In contrast to appellant's assertions that combining the teachings of the references would not achieve the present invention with any reasonable expectation of success,

the following is noted.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This, appellant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young, 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In response to appellant's continued arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones, 21 USPQ2d 1941 (Fed. Cir. 1992).

See the rebuttal in **Sections (2) and (3)** above.

(11) Related Proceedings Appendix.

No decision rendered by a court or Board decision(s) is identified in the Related Appeals and Interferences section of the Examiner's Answer.

As indicated above, a Panel Decision from Pre-Appeal Brief Review, mailed 01/24/2007, for the instant USSN 09/164,568 has been identified in the Related Appeals and Interferences Section of this Examiner's Answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Phillip Gambel/

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